

Public Health Goal for URANIUM in Drinking Water

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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 1 ppb is developed for natural uranium in drinking water based on carcinogenicity. The U.S. Environmental Protection Agency (U.S. EPA) has not established a Maximum Contaminant Level (MCL) for natural uranium. Uranium is a naturally occurring radioactive element that is ubiquitous in the earth's crust. Uranium is found in ground and surface waters due to its natural occurrence in geological formations. The average uranium concentration in surface, ground and domestic water is 1, 3 and 2 pCi/L, respectively. The uranium intake from water is about equal to the total from other dietary components. Natural uranium contains 99.27% ^{238}U , 0.72% ^{235}U and 0.006% ^{234}U . The primary noncarcinogenic toxic effect of uranium is on the kidneys. Uranium is an emitter of ionizing radiation, and ionizing radiation is carcinogenic. On the basis of carcinogenic risks, a PHG of 2 pCi/L is calculated for natural uranium, equivalent to 0.001 mg/L or 1 ppb.

INTRODUCTION

Uranium occurs as a trace element in many types of rocks. Because its abundance in geological formations varies from place to place, uranium is a highly variable source of contamination in drinking water. U.S. EPA has not established a Maximum Contaminant Level (MCL) for natural uranium, but has proposed a health guidance level of 10 pCi/L (Cothorn and Lappenbusch, 1983). U.S. EPA reported in the Federal Register (Fed. Reg. 51: 34836, September 30, 1986) that the Maximum Contaminant Level Goal (MCLG) should be set at zero for natural uranium based on carcinogenicity of ionizing radiation.

There are a number of other standards for uranium (see page 13). These differ from each other and provide equivocal guidance for setting a PHG for natural uranium. The purpose of this document is to review the evidence on toxicity of natural uranium and to derive an appropriate PHG for natural uranium in drinking water.

CHEMICAL PROFILE

Uranium is a radioactive metallic element (atomic number 92). Naturally occurring uranium contains 99.27% ^{238}U , 0.72% ^{235}U and 0.006% ^{234}U . One microgram (μg) of natural uranium has an activity of 0.67 pCi (Cothorn and Lappenbusch, 1983). This is the equilibrium specific activity for natural uranium. Natural uranium in geological formations usually has this specific activity. Natural uranium in drinking water may not be in equilibrium, and therefore its specific activity may vary, as discussed below.

U.S. EPA proposed a definition of the term "natural uranium" as uranium with a varying composition, but typically with the composition given above (Fed. Reg. 51: 34836, September 30, 1986). On an equal weight basis the radioactivity of ^{234}U is 17,000-fold and that of ^{235}U is six-fold greater than that of ^{238}U (NRC, 1980). Uranium may be found in valence states of +2, +3, +4, +5 or +6, but +6 is the most stable form and exists as the oxygen-containing uranyl cation (UO_2^{+2}) (Cothorn and Lappenbusch, 1983).

The best known use of uranium is as a source of fuel for nuclear reactors and nuclear bombs. The fissionable form of uranium is the isotope ^{235}U . This isotope is only a small fraction of naturally

occurring uranium. Several complex minerals are of commercial importance, including carnotite, pitchblende and tobernite (Stokinger, 1981).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

U.S. EPA measured ambient air levels of uranium in 51 urban and rural areas of the United States (U.S.) (U.S. EPA, 1986). The measured concentrations ranged from 0.011 fCi/m³ to 0.3 fCi/m³. Ambient air is unlikely to be a significant source of exposure to uranium outside of mining and occupational settings.

Soil

Uranium is present in soils and rocks in concentrations generally varying between 0.5 and 5 ppm (NRC, 1983). It is found in granites, metamorphic rocks, lignite, monazite sands and phosphate deposits as well as in minerals (Cothorn and Lappenbusch, 1983). Uranium enters other media (air, water and food) from the rocks and soil.

Water

The naturally occurring uranium concentration in drinking water sources depends on factors such as the uranium concentration in the host aquifer rock, the partial pressure of CO₂, the presence of O₂ and complexing agents in the aquifer, the pH and the nature of the contact between the uranium minerals and water (Hess *et al.*, 1985). Uranium in water is derived from phosphate deposits and mine tailings, as well as from run-off of phosphate fertilizers from agricultural land. Greater than 99% of uranium transported by runoff from land to fresh water systems is in suspended particles and remains in the sediment (Cothorn and Lappenbusch, 1983). Environmental pH also influences both the type and relative amount of chemical complexing agents present in solution, which are known to facilitate uranium solubility and mobility.

In 1984 DHS conducted an extensive investigation of radioactivity in ground water in the community of Glen Avon. Four samples had levels greater than 40 pCi/L. Forty-eight samples had uranium activity between 10 and 40 pCi/L. Eight samples had less than 10 pCi/L. Apparently acidic ground water is responsible for mobilizing naturally occurring uranium in the soil (DHS, 1985).

The average amount of uranium in drinking water in the U.S. is 2 pCi/L. Of the 59,812 community drinking water supplies in the U.S., 25 to 650 exceed a uranium concentration of 20 pCi/L; 100 to 2,000 exceed 10 pCi/L; and 2,500 to 5,000 exceed 5 pCi/L (Cothorn and Lappenbusch, 1983).

Some water supplies contain more activity from ²³⁴U than from ²³⁸U, resulting in a ²³⁴U/²³⁸U activity ratio greater than one. It has been observed that the largest disequilibrium ratio occurs in slightly oxidizing environments. The activity ratio is seldom less than one and rarely exceeds two (Cothorn and Lappenbusch, 1983). The radioactivity calculated for ²³⁴U and ²³⁸U, determined by chemical uranium analysis, and using the equilibrium factor of 0.67 pCi/μg, will be in error if the two isotopes are not in equilibrium. The actual factor can range from 0.33 pCi/μg (no ²³⁴U) to at

least 7 pCi/μg ($^{234}\text{U}/^{238}\text{U} = 20$) (Blanchard *et al.*, 1985). U.S. EPA has estimated a specific activity of 1.3 pCi/μg for uranium in drinking water sources based on the results of a nationwide survey (Fed. Reg. 56: 33050-33127, July 18, 1991). The relative abundance of isotopes in a drinking water source depends on physical and chemical factors (such as an oxidizing environment, and the rate of removal of uranium compounds from rocks or soil) and varies greatly from place to place (Cothorn and Lappenbusch, 1983). For this reason U.S. EPA's estimate does not necessarily apply to California drinking water sources. In the absence of data on California drinking water sources, we will use the specific activity of 1.3 pCi/μg which is characteristic of natural uranium in drinking water.

Fluorimetric methods for uranium determination have the necessary sensitivity and accuracy for estimating water concentrations to 10 pCi/L (Blanchard, *et al.*, 1985).

Food

Because uranium is present in many soils and in some water supplies, it also occurs in many foods. The use of phosphate fertilizers increases the uranium level in foods. The National Council on Radiation Protection and Measurements (NCRPM) has estimated that humans take in approximately the same amount of uranium in food as they do in drinking water (NCRPM, 1984). This would suggest a relative source contribution (RSC) in the range of 40 to 60%. OEHHA has chosen to use an RSC of 40% in calculating the PHG.

METABOLISM AND PHARMACOKINETICS

Absorption

Inhalation is a minor route of entry for uranium into humans in the general population. The use of water that contains uranium could expose an individual to uranium by dermal contact or ingestion. Human skin absorption data are not available. Percutaneous absorption has been reported as an effective route of penetration for soluble uranium compounds after application to rat skin (De Rey *et al.*, 1983). Single or daily applications were performed with uranium compounds mixed with emulsion composed of Vaseline® and water (De Rey *et al.*, 1983). The lowest administered dose was one million times higher than the highest concentration of uranium in drinking water found in California.

Gastrointestinal absorption studies of uranium include single oral administration experiments of soluble uranium compounds to rats, dogs, hamsters, baboons and neonatal swine. Because gastrointestinal absorption is consistently lower in rats (less than 0.5%) than in other species studied (Wrenn *et al.*, 1985), experiments on rats are not discussed here. Average absorption was reported to be 1.55% (0.83 to 2.3%) for seven dogs (Fish *et al.*, 1960). Gastrointestinal absorption for adult Syrian hamsters was calculated to be 0.77% (Harrison and Stather, 1981). $\text{UO}_2(\text{NO}_3)_2$ given by gavage to one-day old miniature swine at a dose of 1.5 to 2.0 mg uranium/kg showed absorption of at least 34.5% (Sullivan and Gorham, 1982).

There is limited published information on gastrointestinal absorption of uranium in humans. Hirsch *et al.* (1969) studied oral uranium absorption in four male hospital patients (ages 56 to 78 years). $\text{UO}_2(\text{NO}_3)_2$ (10.8 mg) dissolved in 100 mL Coca Cola® was ingested by each subject after an overnight fast. Urine and fecal samples were collected and analyzed for uranium. The four

subjects showed uranium absorption of 0.3%, 0.7%, 1.1% and 3.3%. Unabsorbed uranium passes into the feces. Daily excretion of uranium in urine approximates the uranium absorbed from food and drink. Hirsch and Spoor (1973) cited data indicating that between 12% and 30% of uranium ingested in the normal diet is absorbed from the gastrointestinal tract. The levels of natural uranium in food and water are lower than those used experimentally.

In general, the smaller the amount of uranium ingested, the greater the fraction absorbed (Wrenn *et al.*, 1985). On the basis of a U.S. survey (Welford and Baird, 1967) it was estimated that the intake of uranium from the normal diet is 1.75 µg/day, and that the extent of gastrointestinal absorption was 7.7% (Wrenn *et al.*, 1985). Fisher *et al.* (1983) reported that uranium absorption for three controls was 0.6% to 1% and for three retired uranium workers it was 0.55% to 1.6%. Somayajulu *et al.* (1980) collected urine and feces in summer and winter from one individual. The estimated uranium absorption for the summer sample was 3.8% and for the winter sample was 0.57%. Wrenn *et al.* (1985) using data from three human studies and six animal experiments, gave a best estimate of gastrointestinal absorption of uranium for adult humans at environmental levels of uranium intake of 1.4%. No values for human neonates were given. Gastrointestinal absorption of ²³⁸Pu (plutonium) was about 100 times higher in neonatal rodents than in adult rodents and this difference was 10 to 20 times greater in swine (Sullivan, 1980). Absorption of uranium by neonatal swine is higher than absorption of Pu from the gastrointestinal tract (Sullivan and Gorham, 1982).

Enhanced permeability of the intestine of the neonate facilitates passage from the nursing mother's milk to the neonate of macromolecules that are essential to immunity (Sullivan and Gorham, 1982). Uranium may be associated with proteins during passage across the intestinal mucosa. Absorption of iron and other heavy metals increases during lactation (Batey and Galagher, 1977; Bhattacharya *et al.*, 1981 and 1982; Kostial and Momcilovic, 1972). Certain dietary constituents can enhance the absorption of lead (Blake, 1983) and cadmium (Smith and Foulkes, 1985). Therefore it is reasonable to assume that sensitive members of a population may have higher gastrointestinal absorption of uranium than healthy adults.

In its review of the literature, U.S. EPA found values for gastrointestinal absorption of uranium in humans ranging from 1% to 30% (U.S. EPA, 1991a, b). For purposes of calculating the cancer risk of natural uranium in drinking water, U.S. EPA chose 20% as the "best estimate" acknowledging that there is "substantial uncertainty" associated with this number (U.S. EPA, 1991a, b).

Distribution and Excretion

Bicarbonate complexes are the chief form in which uranium is absorbed and transported within the body (Hodge, 1973). $\text{UO}_2(\text{HCO}_3)_2$ in plasma is taken up by bone and filtered by the glomeruli into the urine (Durbin and Wrenn, 1975). Most of the studies involving distribution and excretion of uranium have been based on administration by intravenous or intraperitoneal injection, feeding or inhalation to animals. Stevens *et al.* (1980) measured the distribution, retention and excretion of ²³³U in seven beagles injected intravenously with 2.8 µCi ²³³U per kg body weight, and sacrificed at times ranging from 1 to 726 days post injection. Twenty-two percent of the injected uranium was found in the kidney at one day post injection with high concentrations localized in the proximal tubules and 7.7% of the uranium was found in the skeleton.

The kidneys and bones are the principal sites of accumulation and toxic action of uranium (Yuile, 1973; Stevens *et al.*, 1980; Morrow *et al.*, 1982). Following uranium administration, 80% is excreted in urine and feces, 10% is deposited in the kidneys and the remaining 10% is deposited in the skeleton with negligible concentrations appearing in other tissues (NRC, 1983). The skeleton is the major site of long-term storage of uranium (Wrenn and Singh, 1982).

Several studies have reported the amount of uranium in the skeleton of persons with no known occupational exposure to uranium. The average values ranged from 2.3 to 61.6 µg with a mean value of 24.9 ± 22 µg uranium in 5,000 grams of bone (Wrenn *et al.*, 1985).

There is a fast and a slow phase of uranium excretion in humans and animals. The retention half-lives of uranium in bone and kidney are of most relevance. For bone, half-lives of 883 days (Stevens *et al.*, 1980), 180 and 360 days (Hursh and Spoor, 1973) and 800 days (Bernard, 1958) have been reported. Retention half-lives for uranium in human kidney have been reported as 30 days (Bernard, 1958) and more recently as 6 days and 1,500 days for the fast and slow components, respectively (ICRP, 1979). Wrenn *et al.* (1985) utilized a 15-day half-life (Hursh and Spoor, 1973) and this value was incorporated into the uranium pharmacokinetic model.

TOXICOLOGY

Toxicological Effects in Animals

Numerous animal studies of the toxicity of uranium have been undertaken, beginning with the Manhattan Project in the 1940s. These studies have been reviewed by Yuile (1973). More recently, the toxicology of uranium in animals has been reviewed by Durbin and Wrenn (1975) and by Wrenn *et al.* (1985).

Acute Toxicity

The acute oral toxicity of uranium compounds is low. There are large differences in sensitivity to uranium among the species tested. The LD₅₀s of intraperitoneal uranium nitrate ranged from 0.1 to 0.3 mg/kg in the rabbit and guinea pig to as much as 20 to 25 mg/kg in mice (Durbin and Wrenn, 1975). The approximate lethal doses of UO₂(NO₃)₂ administered intravenously to four species are given in Table 1.

Table 1. Lethal Doses of Uranium

Species	Lethal Dose (mg uranium/kg)	Dose Ratio
rabbit	0.1	1
guinea pig	0.3	3
rat	1.0	10
mouse	10 to 20	100 to 200

Nine days after a single intravenous injection of 2.8 µCi ²³³U/kg or 2.8 µCi natural uranium/kg, a marked elevation of the blood urea nitrogen (BUN) was observed in all dogs tested (Stevens *et al.*, 1980). Two episodes of azotemia (retention in the blood of excessive amounts of nitrogenous compounds) were noted. The first increase in BUN was attributed to chemical toxicity rather than

radiation-induced toxicity because a similar effect was observed in the dogs given natural uranium instead of ^{233}U . Nine weeks after injection, a secondary episode of azotemia occurred in the dogs injected with ^{233}U , but not in the dogs injected with natural uranium. The authors hypothesized that the secondary increase may have been radiation-induced. Stevens *et al.* (1980) commented that following prolonged exposure of beagle dogs to ^{232}U or ^{233}U , the skeleton and not the kidney may be the primary target organ and osteosarcoma may be the cause of death.

Subchronic and Chronic Toxicity

Noncarcinogenic Effects

In a study of 30 dogs administered $\text{UO}_2(\text{NO}_3)_2$ (Yuile, 1973) in the diet for one year at dose levels of 0.0002 to 10 g/kg, adverse effects on growth were noted only for those dogs receiving 0.2 g/kg of uranyl nitrate.

Morrow *et al.* (1982) published inhalation studies with uranium on dogs. They found that an absorbed dose of approximately 10 $\mu\text{g/kg}$ body weight produced renal injury and proposed that a concentration of 0.3 $\mu\text{g/g}$ kidney is the threshold concentration for renal injury in dogs. The mechanism of toxic action on the kidney postulated by Hodge (1973) and Nechaey *et al.* (1981) was that UO_2^{++} may compete with Mg^{++} and Ca^{++} at ATP binding sites for these metals, thus disrupting active transport across the cell membrane.

Studies conducted from one day to five years showed that dogs, monkeys and rats could breathe a $\text{UO}_2(\text{NO}_3)_2$ aerosol at 5.8 mg/m^3 of air with little evidence of serious injury (Leach *et al.*, 1970). Following the five-year exposures, groups of animals were held for postexposure study as long as 6.5 years (Leach *et al.*, 1973). Pulmonary neoplasia developed in a high percentage of the dogs examined two to six years after exposure. Pulmonary and tracheobronchial lymph node fibrosis was more marked in monkeys than in dogs.

Novikov (1970) pointed out that acute and chronic uranium poisoning produces disturbances, not only in the kidney, but also in the cardiovascular system, the blood and hematopoietic system, the immune system, the thyroid, adrenal gland and liver, and in basal metabolism. Novikov (1970) stated that the use of the uranium concentration in the kidney as the sole criterion of toxicity is untenable because of toxicity in other organ systems. Novikov and Yudina (1970) examined the effects of 0.02, 0.2 and 1.0 mg/kg of uranium administered *per os* for 12 months to rabbits. They observed no changes in serum urea, creatinine and chloride levels. A dose of 1.0 mg/kg inhibited nucleic acid metabolism in rabbit kidney and liver.

Braunlich and Fleck studied the nephrotoxicity of uranyl nitrate in rats of different ages (1981). They found that alkaline phosphatase in the urine was a good indicator of nephrotoxicity for all rats except the very young and old (Braunlich and Fleck, 1981).

Reproductive and developmental effects have been studied in rodents by several groups of investigators. These studies are summarized in U.S. EPA's drinking water criteria document (U.S. EPA, 1991b). In general, uranium salts do cause reproductive and developmental effects (e.g., embryoletality, malformations and testicular effects) but only when administered at much higher doses than those that would cause nephrotoxicity.

Carcinogenic Effects

Sarcomas resulted in rats injected with metallic uranium in the femoral marrow and in the chest wall (Hueper *et al.*, 1952). The authors were unable to determine whether the local tumors induced by uranium were caused by metallocarcinogenic or radiocarcinogenic action. Alpha-emitting, bone-seeking radionuclides such as ^{232}U , ^{233}U and ^{226}Rn have been shown to induce bone tumors in rodents (U.S. EPA, 1991a, b). In general ionizing radiation is regarded by U.S. EPA as carcinogenic in animals and humans (U.S. EPA, 1991a, b).

Toxicological Effects in Humans

Acute Toxicity

One case study reported two deaths of human beings accidentally exposed to uranium hexafluoride and its breakdown products (uranyl fluoride and hydrofluoric acid) by inhalation (ATSDR, 1990). The acute effects of this exposure were characteristic of hydrofluoric acid exposure. No studies were found of acute effects to humans resulting from oral exposure to uranium or uranium compounds. Levels of $\text{UO}_2(\text{NO}_3)_2$ below 70 $\mu\text{g/kg}$ administered intravenously to six terminally ill patients (Hursh and Spoor, 1973) did not produce renal injury as evidenced by changes in urinary proteins and catalase.

Chronic Toxicity

Noncarcinogenic Effects

The human data on uranium toxicity have been summarized by Hursh and Spoor (1973), Adams and Spoor (1973) and by Boback (1975). Boback (1975) found no abnormal clinical chemistry parameter effects in urine from uranium workers involved in exposure incidents which produced urinary uranium concentrations up to 2.85 mg/L. Clarkson and Kench (1952) found low but significantly elevated levels of amino acids in the urine of 12 workers exposed to uranium hexafluoride.

Short-term follow-up studies in the 1940s and 50s of uranium workers exposed for several months or years to high levels of soluble uranium compounds showed only transient kidney damage (proteinuria) and no evidence of permanent effects (Hursh and Spoor, 1973).

Moss and McCurdy (1982) reported that increased $\beta_{2\mu}$ -globulin excretion in urine could be correlated with uranium in drinking water at concentrations up to 0.7 mg/L. There are neither histories of, nor overt clinical signs of kidney dysfunction even among those drinking water with the highest uranium concentration. No subtle changes in kidney function were revealed by clinical chemistry. Wrenn and Singh (1981) concluded that the skeleton is the major site of storage of uranium, but the kidney is the principal site of uranium injury after it once gains entrance to the circulation. More recently, Thun *et al.* (1985) found significantly higher urinary excretion of $\beta_{2\mu}$ -globulin and five amino acids in uranium workers than in a reference group. Increased renal excretion was associated with length of exposure to soluble uranium. These data were consistent with uranium-induced nephrotoxicity.

Uranium has a pronounced tissue toxicity quite apart from its potential toxicity to the skeleton. Chen *et al.* (1961) concluded that ^{238}U would not pose a radiological hazard in humans because the quantities necessary to deposit sufficient uranium in bone to cause radiation effects would be far in excess of the uranium doses causing lethal renal damage. More recent analyses of the potential carcinogenic effects of natural uranium due to ionizing radiation do not agree with this conclusion (U.S. EPA, 1991a, b).

Carcinogenicity

A mortality study was conducted on 2,731 males employed at a uranium refining and processing facility. Exposure and smoking habits were not analyzed. No deaths occurred from cancers of the bone or thyroid, but deaths from cancer of the esophagus showed a statistically significant increase (Dupree, 1980).

In uranium miners an increased mortality from lung cancer has been recognized for many years (Pochin, 1985). Lung cancer has been related to the radiation dose to lung tissues. The dose to the lung in uranium mines comes essentially from the radioactive decay products of the radioactive gas radon, rather than from uranium itself. The atmosphere in mines is likely to contain materials such as arsenic and diesel fume polycyclic aromatic hydrocarbons, which have significant carcinogenic effects. These would have confounding effects on any study of the carcinogenicity of uranium itself.

The cigarette smoking habits of the miners also need to be determined and accounted for in the epidemiological risk assessment. It should be noted that other types of underground mining including iron, lead and fluorspar have also been associated with radon gas-induced lung cancer (Zeise *et al.*, 1987). Therefore, at the present time inhalation of uranium *per se* cannot be considered carcinogenic for humans.

Polednak and Frome (1981) described mortality in a cohort of 18,869 white males who were employed between 1943 and 1947 at a uranium conversion and enrichment plant in Oak Ridge. Standardized mortality ratios (SMRs) for various sites, including lung cancer, bone cancer, leukemia and disease of the respiratory and genitourinary system did not tend to be higher in workers exposed to the highest average levels of uranium dust. Workers in the “alpha chemical department” were exposed to the highest levels of airborne uranium dust. There were no deaths from bone cancer or leukemia, or from chronic nephritis. SMRs for lung cancer were analyzed by age at hire and job classification. The SMR for lung cancer in these alpha chemistry workers hired at ≥ 45 years of age was high, based on small numbers. None of the seven lung cancer decedents worked for one year or longer in alpha chemistry.

There are no reports of experimental induction of bone cancer by ingested, injected or inhaled natural uranium in soluble form (Wrenn *et al.*, 1985). However, bone cancer has been induced in experimental animals by injection or inhalation of soluble compounds of high specific activity uranium isotopes, ^{232}U and ^{233}U (Finkel, 1953). Lung cancer was produced in rats and dogs, but not in monkeys following continuous inhalation of large amounts of highly soluble UO_2 for two to five years (Leach *et al.*, 1970; Leach *et al.*, 1973).

Wilkinson (1986) has reported that several counties in northern New Mexico displayed high rates of mortality from gastric cancer. Significant differences in sex-specific, age-adjusted, average annual stomach cancer mortality rates among white humans during 1970 to 1979 were found

between counties with significant deposits of uranium compared to those without significant deposits (Wilkinson, 1986). The identification of uranium deposits is based on a qualitative survey designed to identify areas containing uranium deposits that might be of commercial value. Wilkinson (1986) advanced a working hypothesis that residents of counties with significant deposits of uranium are exposed to higher levels of radionuclides such as radon and radon daughters than residents of counties lacking the uranium deposits.

Genotoxic and Cytotoxic Effects

Uranium miners have been found to have increased frequency of chromosomal aberrations in human lymphocytes, but these have been thought to be due to radon or its radioisotope daughters (Brandom *et al.*, 1978; ATSDR, 1990). Other genotoxic effects have not been adequately tested (ATSDR, 1990).

Blood lymphocyte cultures from two groups of workers exposed to uranium were examined for asymmetric chromosomal aberrations and sister-chromatid exchanges (SCEs). Significant increases were seen in both of these cytogenetic endpoints (Martin, *et al.*, 1991). These investigators interpreted their results as evidence of clastogenic effects of uranium.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Novikov and Yudina (1970) examined the effects of 0.02, 0.2 and 1.0 mg/kg of uranium administered *per os* for 12 months to rabbits. They observed no changes in serum urea, creatinine and chloride levels. A dose of 1.0 mg/kg inhibited nucleic acid metabolism in rabbit kidney and liver. This effect is probably related to general toxicity to these two organs. The no-observed-adverse-effect-level (NOAEL) in this study was 0.2 mg/kg body weight in rabbits. The lowest-observed-adverse-effect-level (LOAEL) was 1.0 mg/kg for nucleic acid metabolism effects in the liver and kidneys.

Carcinogenic Effects

U.S. EPA has classified natural uranium as a Group A carcinogen (“human carcinogen based on sufficient evidence from epidemiological studies”) because it is an emitter of ionizing radiation. U.S. EPA classifies all emitters of ionizing radiation as Group A carcinogens. U.S. EPA acknowledges that “studies using natural uranium do not provide direct evidence of carcinogenic potential.” However, studies with radium and certain isotopes of uranium provide evidence for the carcinogenicity of ionizing radiation in humans (U.S. EPA, 1991a, b).

Mays *et al.* (1985) estimated the lifetime cancer risk of daily intake of uranium in drinking water based on data from induction of skeletal cancers by radium isotopes. They estimated that exposure of one million persons to 5.0 pCi per day from uranium isotopes in drinking water would be expected to result in 1.5 additional bone sarcomas. This is equivalent to a cancer risk for uranium in drinking water of 6.0×10^{-7} per pCi/L (assuming consumption of two liters of water per day). This is virtually identical to the U.S. EPA’s recent estimate based on the RADRISK model (see below).

U.S. EPA has calculated a carcinogenic potency for natural uranium based on “effects of ionizing radiation generally, the similarity of uranium to isotopes of radium and on the effects of high activity uranium” (U.S. EPA, 1991a). According to U.S. EPA’s calculation, uranium in drinking water poses a cancer risk of approximately 5.9×10^{-7} per pCi/L. Based on this estimate of cancer risk, U.S. EPA’s proposed MCL of 20 pCi/L corresponds to a lifetime cancer risk of 1×10^{-5} (U.S. EPA, 1991a).

CALCULATION OF PHG

Noncarcinogenic Effects

An uncertainty factor of 100 is used when human data are not available, and when extrapolating from valid results of long-term studies in animals (Fed. Reg. 50: 46946, November 13, 1985). This overall uncertainty factor is made up of 10-fold for inter-species variability, and 10-fold for human variability.

A public health-protective concentration (C) for uranium in drinking water (in mg/L) can be calculated following the general equation for noncarcinogenic endpoints:

$$C = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{L/day} \times \text{UF}}$$

where,

NOAEL	=	No-observed-adverse-effect-level (0.2 mg/kg-day for kidney effects in rabbits)
BW	=	Body weight default for an adult male (70 kg)
L/day	=	Daily water consumption for an adult (2 L/day)
RSC	=	Relative source contribution of 40% (0.4)
UF	=	Uncertainty factor of 100 (10-fold for inter-species variability and 10-fold for human variation)

therefore,

$$C = \frac{0.2 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.4}{2 \text{ L/day} \times 100} = 0.028 \text{ mg/L} = 0.03 \text{ mg/L (rounded)} = 30 \text{ ppb.}$$

The C value of 0.3 mg/L is equivalent to approximately 40 pCi/L (based on a specific activity of 1.3 pCi/μg).

Repeating the same calculation for a child:

$$C = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{L/day} \times \text{UF}}$$

where,

NOAEL	= Same as for the adult calculation
BW	= An assumed default child's body weight (10 kg)
L/day	= Daily water consumption for a child (1 L/day)
RSC	= Relative source contribution of 40% (0.4 as for the adult)
UF	= Uncertainty factor of 100 (as for the adult).

Therefore,

$$C = \frac{0.2 \text{ mg/kg-day} \times 10 \text{ kg} \times 0.4}{1 \text{ L/day} \times 100}$$
$$= 0.008 \text{ mg/L} = 8 \text{ ppb.}$$

The health-protective concentration based on noncarcinogenic effects is 0.008 mg/L is equivalent to 10 pCi/L.

Carcinogenic Effects

U.S. EPA estimated the carcinogenic potency of natural uranium using the RADRISK dosimetric model (U.S. EPA, 1991a,b). To perform this calculation, U.S. EPA assumed an adult drinking water consumption of two liters per day, and a gastrointestinal absorption factor of 20%. The cancer potency arrived at in this way is 5.9×10^{-7} per pCi/L. We concur with this estimate of cancer potency for natural uranium in drinking water.

Based on the above estimate of cancer potency, the drinking water level corresponding to a *de minimis* theoretical excess individual excess cancer risk of 1×10^{-6} would be 1.7 pCi/L (U.S. EPA, 1991a). This can be rounded off to 2 pCi/L. Dividing 1.7 pCi/L by the specific activity of 1.3 pCi/μg would be 1.3 μg/L or rounded off to 1 ppb. Therefore, based on carcinogenic risks of ionizing radiation, the most health-protective concentration for uranium in drinking water is 2 pCi/L, equivalent to 0.001 mg/L (1 ppb).

Therefore, OEHHA calculates a PHG of 1 ppb for uranium in drinking water.

RISK CHARACTERIZATION

The PHG of 1 ppb (2 pCi/L) for natural uranium in drinking water is based on the carcinogenic risks of ionizing radiation, which corresponds to a *de minimis* theoretical excess individual lifetime cancer risk level of 1×10^{-6} . For risk management purposes, drinking water levels of 20 pCi/L (10 ppb) and 200 pCi/L (100 ppb) would correspond to theoretical individual excess lifetime cancer risks of 1×10^{-5} and 1×10^{-4} , respectively. The 10^{-6} cancer risk-based public health-protective concentration of 1 ppb is adopted as the PHG because it results in a lower, more health-protective PHG than nephrotoxicity. This PHG would also be protective against reproductive and developmental effects which have been observed in rodent experiments.

A number of assumptions had to be made in calculating this PHG. Each of these assumptions is a source of uncertainty. It was assumed that ionizing radiation (particularly alpha particles) emitted by natural uranium would be equally as carcinogenic as ionizing radiation emitted by more

radioactive substances. The extrapolation from high-dose to low-dose was performed using the RADRISK model (U.S. EPA, 1991a, b). This assumption and extrapolation is the source of some uncertainty. It is noteworthy that Mays *et al.* (1985) arrived at a virtually identical estimate of the cancer potency of uranium, based on a different methodology.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using UFs, body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20% to 80% (0.2 to 0.8) depending on the available scientific evidence.

U.S. EPA follows a general procedure in promulgating MCLGs:

1. if Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,
2. if Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range,
3. if Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

Gastrointestinal absorption of uranium for humans was assumed to be 20%. The range of values identified in the literature is 1% to 30% (U.S. EPA, 1991a, b). Actual gastrointestinal absorption may vary from individual to individual.

Standard default assumptions of 70 kg body weight for adults, and two liters per day drinking water consumption were made. Actual body weights and drinking water consumptions vary over a wide range.

Ionizing radiation has been conclusively shown to be carcinogenic in humans, which is why U.S. EPA classifies all emitters of ionizing radiation as Class A carcinogens. There can be little doubt that high levels of natural uranium in drinking water would present a cancer risk to humans who consume such water over a long period of time. To avoid this risk, a PHG has been proposed based on the ionizing radiation emitted by natural uranium.

OTHER STANDARDS AND REGULATORY LEVELS

U.S. EPA has proposed an MCLG of 0 pCi/L for uranium, based on their classification of it in Carcinogen Group A (FR 56, 33050, July 18, 1991). U.S. EPA also reported an adjusted acceptable daily intake (AADI) of 60 µg/L, or 40 pCi/L.

U.S. EPA has also proposed an MCL of 20 µg/L (equivalent to approximately 30 pCi/L, based on a specific activity of 1.3 pCi/µg (Fed. Reg. 56: 33050, July 18, 1991). This proposed MCL corresponds to a cancer risk of 1×10^{-5} , as estimated by U.S. EPA. Economic and technical feasibility were considered in arriving at this proposed MCL. This proposed MCL has never been made final.

The State of California adopted an MCL of 20 pCi/L for natural uranium based on kidney toxicity to adults (Lam *et al.*, 1994; DHS, 1987).

In the latest review by the National Research Council (NRC, 1983), a suggested no-adverse-response-level (SNARL) in drinking water for chronic exposure of 35 µg/L (23 pCi/L) was based on noncarcinogenic responses to adults. The National Workshop on Radioactivity in Drinking Water recommended that the limiting concentration for natural uranium in drinking water should be 100 µg/L (67 pCi/L) (Wrenn *et al.*, 1985).

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